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International and temporal comparative analysis of UK and US drug safety regulation in changing political contexts

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ABSTRACT

Modern UK drug regulation began in 1971. In view of significant neo-liberal political reforms to drug regulation in the UK and US since the early 1990s, this article compares the performance of UK and US drug safety regulation during both 1971–1992 and 1993–2004, by investigating drug safety withdrawals (DSWs). Combined quantitative and comprehensive qualitative regulatory case history methodology is employed to explain comparative trends in DSWs and relate them to the key claims of central regulatory theories. It is found that there was a dramatic increase in DSWs in the US during 1993–2004 compared with 1971–1992, and a major increase in the extent to which drugs withdrawn on safety grounds in the UK were left on the US market. Analysis reveals that these findings are best explained by changes in institutional regulatory culture at FDA, consequent upon neo-liberal reforms during 1993–2004, which meant that US regulators adopted more permissive interpretations of safety signals and associated risk-benefit assessments leading to more unsafe drugs being approved on to the US market than during 1971–1992. Changes in the UK are less marked because it already embraced a relatively permissive regulatory culture during 1971–1992 and neo-liberal reforms post-1992 were more attenuated. It is concluded that the changes support corporate bias theory, and that, to improve patient protection, drug safety regulation in the UK and US should shift direction towards the US regulatory model of 1971–92.

1. Background and objectives

Government pharmaceutical regulation is important to prevent patients from exposure to harmful unsafe drugs whose risks outweigh their benefits. The last 25 years has seen an increase in international studies of prescription drug safety regulation (Abraham and Lewis, 2000, Abraham and Reed, 2001; Daemmrich, 2004; Wiktorowicz, 2003; Wiktorowisz et al., 2012, 2018). However, confined to descriptions of regulatory processes/standards, these studies are inconclusive about the implications of policy arrangements for drug safety/regulatory *outcomes*. Other significant political/organisational analyses of drug safety regulation include Angell (2004), Carpenter (2010), Light (2010), Goldacre (2012), Lexchin (2016) and Light and Maturo (2015) but each is limited to a single nation. International comparisons of UK and US drug safety regulatory processes *and* outcomes are available, but outcome analyses neither span beyond the mid-1990s nor involve comprehensive drug cohorts (Abraham, 1995, Abraham and Sheppard, 1999).

Yet, since 1990 the socio-political terrain of UK and US drug regulation has changed considerably. Modern UK drug regulation began in 1971 under extreme state secrecy of the 1968 Medicines Act, but the 1992 UK Code on Access to Government Information and the 2000 UK Freedom of Information (FOI) Act slightly increased transparency and accountability of British drug regulation, though legislative oversight by UK and EU Parliaments remained minimal during 1993–2004 (House of Commons Health Committee, 2005). From 1989, the UK drug regulatory authority was transformed into the Medicines Control Agency (MCA) until 2003 when it became the Medicines and Healthcare Products Regulatory Agency (MHRA). Following UK Government policy, from 1989, the British regulatory authority shifted from being funded equally by direct taxation and fees from the pharmaceutical industry to being funded 100% by industry fees. Pharmaceutical companies agreed to the arrangement in exchange for shortening drug regulatory review times at MCA. The first MCA director, who came from industry, instigated an enduring policy of making the regulatory agency more responsive to industry demands by cutting drug review times by 24% in one year and increasing consultation between industry and regulators (Abraham and Lewis, 2000:60-76).

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Significantly, in 1995, the European Medicines Agency (EMA), was established to administer an EU-wide 'centralised' regulatory procedure (CP) for most innovative drugs, drawing on its expert Committee on Human Medicinal Products (CHMP) to make regulatory decisions. Consequently, many new drugs, including some drugs in our cohort, entered the UK market via *EMA-CHMP regulatory decisions*. EMA is funded by industry fees rising from 20% in 1995 to 75% in 2010 (Davis and Abraham, 2013). It publishes reports justifying centralised EU approvals, thus increasing the accountability of regulatory decision-making regarding many new drugs entering the UK market after 1995 (Abraham and Lewis, 2000).

Meanwhile, in the US, the 1992 Prescription Drug Users Fee Act (PDUFA) was introduced because Congress, which had previously funded the US drug regulatory agency (FDA), entirely from direct taxation, refused to fund it adequately. PDUFA saw FDA become increasingly funded by industry fees reaching 50% by 2002 and over 60% by 2010 (Davis and Abraham, 2013; Josefson, 2002). To receive this funding, statutory drug review deadlines were introduced requiring FDA to cut its review times dramatically. Funding renewal every five years was conditional on making such cuts to the satisfaction of Congress and the pharmaceutical industry. PDUFA funds had to be spent on regulatory review and not post-market safety surveillance or FOI requests (whose responsiveness declined). Between 1993 and 2008, FDA shortened drug review times by more than half so by 1994 it was approving drugs faster than MCA (Davis and Abraham, 2013; Government Accounting Office [GAO] 1995:11; Olsen, 2013). While in 1988 only 4% of new prescription drugs introduced on to the world market were first approved by FDA, by 1998 this had risen to 66% (Willman, 2000).

After PDUFA and the 1997 FDA Modernisation Act (FDAMA), further changes ensued, such as increased industry consultation with FDA on new drugs under review; inclusion of (non-voting) industry participation on FDA expert advisory committees; and approval of some new drugs based on significantly less clinical trial evidence via expedited pathways (FDA, 1998a; 1998b; 2000; Lurie and Sasich, 1999). Between 1994 and 2004, Congress rarely held hearings about FDA's performance in assessing drug safety, as it had done during the 1970s and 1980s, but instead persistently interrogated the agency about how it could accelerate approval of new drugs.

An important policy question, therefore, is whether drug safety regulatory outcomes have altered since these changes in political context, and if so, what explanatory relationship, if any, exists between the two. The answer to that question can then empirically ground the answer to the social scientific question of which main regulatory theory best characterises these changes: neo-liberal theory that they have been in the interests of public health; disease-politics theory that they have been driven by patient demand; capture theory that regulatory agencies have drifted away from their mandate to protect public health towards promoting industry interests instead; or corporate bias theory that regulatory agencies and Executive/Legislative arms of Government have combined to prioritise industry interests over those of public health (Abraham, 1995, Abraham and Lewis, 2000, Davis and Abraham, 2013; Carpenter and Moss, 2014; Lexchin, 2016).

Several quantitative input-outcome studies of US drug regulation have examined statistical associations between discretely defined *regulatory inputs*, such as industry fees; reduced review-times (including expedited pathways); and/or near-deadline approvals, on the one hand, and post-market *regulatory outcomes*, on the other, such as number of drug safety withdrawals (DSWs) – i.e. drugs approved on to the market by a government regulatory authority, but then subsequently removed from that market for safety reasons by the regulatory agency or manufacturer; safety-related changes to drug labelling (e.g. warnings); and/or regulatory-communications to healthcare professionals. The US Government Accountability Office [GAO] (2002) reported that post-PDUFA reductions in review times were correlated with more US DSWs and Mostaghim et al. (2017) demonstrated a statistical association between shorter FDA review-times and increased adverse safety-related labelling changes. However, Berndt et al. (2005), Carpenter et al. (2008) and Downing et al. (2017) recorded no association between US DSWs and FDA review-times *per se*, though the latter two found a statistical association between near-deadline approvals and increased US DSWs/safety-warnings. We found no input-outcome studies of UK drug safety regulation, though Zeitoun et al. (2015) reported no quantitative correlation between near-deadline approvals/reduced review-time and DSWs at EU level.

These input-outcome investigations provide temporal comparison relating to political change *within* single-nations/territories, but no international comparative analysis. Moreover, exclusive emphasis on input-outcome quantitative associations offers little understanding of the *processes* of regulatory assessment, such as medico-scientific knowledge/evidence available to regulators and the weighing up that evidence within regulatory decisions/actions. Yet such social scientific understanding is vital to make rational judgements about the public-health-protective performance of regulation. For example, if a regulatory agency enforces more DSWs after a political intervention (e.g. introduction of industry fees) than before, then that could be because, in the later period, the agency is approving more unsafe drugs (public-health-endangering) or because it has become stricter in policing post-market safety (public-health-protective). Furthermore, it is impossible to judge whether leaving a drug on the market, while adding a warning, rather than withdrawing it, is a safety-protective or safety-endangering regulatory measure without case-study analysis of the regulatory assessment involved. Case-study analysis is also needed because there is no such thing as a typical DSW – regulatory decisions are made on a case-by-case basis, although the possibility of a DSW decision should always arise where a product's risks are deemed to outweigh its benefits. This usually emerges due to pre-market or post-market evidence of adverse drug effects on patient safety, known as safety signals (e.g. heart attacks, liver dysfunction, arrhythmia, mortality).

Only Abraham and Davis (2005) have conducted an international comparative analysis combining quantitative comparisons and comprehensive case-study analyses of all DSWs in more than one country (UK and US). However, their comparison was confined to 1971–1992 and solely spatial. In this paper, we follow Abraham and Davis's (2005) approach of quantitative comparisons combined with qualitative regulatory case-history scrutiny of each DSW and go beyond it by comparing the UK with the US *before and after* significant political changes evident in both countries.

Abraham and Davis (2005) demonstrated that there were over twice as many UK DSWs as US DSWs during 1971–1992 because FDA imposed more stringent safety standards, especially by approving fewer unsafe drugs on to the market than the British regulatory authorities. The policy implication was that more stringent US drug safety regulation (1971–1992) delivered additional safety protection relative to the UK, even if it approved drugs slower than UK regulators. The FDA's greater stringency compared with UK regulatory authorities in that period was explained by a more critical institutional stance towards the pharmaceutical industry due to: more legislative (Congressional) oversight on how well FDA protected citizens from unsafe drugs; a more minimal role for industry consultation and outside expert advisers with industry conflicts of interest to influence regulatory decisions; and greater public/legal accountability, via extensive (FOI) legislation (1967 US FOI Act).

Here, we compare UK and US DSWs from 1993 to 2004 inclusive and investigate how DSWs have changed compared with 1971–1992. Drawing particularly on our qualitative case-study analyses, we then systematically provide social scientific explanations for those changes. Our time-period selection is explicitly linked to political context. Like Olsen (2013), we consider 1993–2004 because after the 2004 rofecoxib (Vioxx) arthritis drug disaster, estimated to have caused over 60,000 heart attacks in both countries, further changes to pharmaceutical regulation occurred, which merit separate study (Institute of Medicine, 2006). Nonetheless, lessons from the 1993–2004 period provide crucial

insights into many regulatory policy challenges that still obtain.

2. Methods and data sources

Extensive documentary data were collected on all drugs withdrawn from the UK and/or US markets from 1993 to 2004 inclusive. For quantitative temporal analyses (allowing for a four-year follow-up period explained below) we collected DSW data with a cut-off date of 2008. We employed two core analytical methodologies: (1) quantitative surveys and analyses of all DSWs; and (2) comprehensive qualitative case-study analysis of all drugs in the sample to clarify/extend findings beyond quantified trends, to discover reasons for DSWs in relation to how evidence was assessed within regulatory decision-making processes. Fieldwork spanned many years in both countries from mid-2000s. We sometimes refer to 'UK/EU regulators' because some UK DSWs were made by UK regulators alone, but others by EMA for drugs approved EU-wide after 1995.

Data on individual drugs were collected and reviewed from: PubMed, Web of Science and ASSIA; *Scrip World Pharmaceutical News*; WHO databases; publicly-available court documents; pharmaceutical manufacturers' websites; FDA drug-approval packages; US Federal Register; Medwatch safety-related drug label changes; Public-Health Advisories and Dear Healthcare Professional letters; transcripts of FDA advisory committee meetings; FDA publications, including Center for Drug Evaluation and Research (CDER) *Report to the Nation, FDA Consumer,* and PDUFA-related reports to Congress; Congressional hearings; MCA and MHRA publications, such as *Current Problems in Pharmacovigilance* and *Drug Safety Update*; MHRA website; publicly-available minutes of meetings of UK Committee on Safety of Medicines and its Sub-Committees; annual reports of MCA, MHRA and their expert advisory committees; Association of the British Pharmaceutical Industry (ABPI) Compendium of Data Sheets and Summaries of Product Characteristics until 1999 and Medicines Compendium after 1999; UK FOIA requests to MHRA; European Public Assessment Reports; safety alerts, press releases, expert opinions, and minutes of meetings of EMA's CHMP. A list of all UK and US DSWs from 1993 to 2008 was compiled from these databases and relevant published surveys (Berndt et al., 2005; Carpenter et al., 2008; CDER, 2006; Fung et al., 2001; Tufts, 2005).

2.1. Numbers of DSWs by approval and withdrawal dates

Counting DSWs is complex. From 1993 to 2008, there were 38 DSWs in the UK, US or both (Table 1). Consistent with Abraham and Davis's (2005) criteria, these include all new molecular entities (NMEs), new formulations/combinations of NMEs, and any products containing a new isomer/ester/salt, but exclude new dosage forms. Table 1 also presents DSWs subsequently re-instated. Abraham and Davis (2005) excluded re-instated drugs. To be consistent with their analysis, we also *exclude* re-instated drugs from our *quantitative* comparisons regarding numbers of DSWs, DSW rates, and divergent regulatory outcomes, but we *include* them in our *qualitative* case-study analysis of decision-making processes. Table 1 includes five drugs withdrawn in 1993–2004, which were originally marketed in the UK before 1971 ('pre-licensing') because they were subsequently granted full product licences under modern UK drug regulation. Additionally, we have updated Abraham and Davis (2005) for the period 1971–1992 with a 2008 cut-off date.

Every DSW may be identified either by when it was approved on to the market (approval date) or when it was withdrawn from the market (withdrawal date). After approval, it generally takes some time for a drug to be withdrawn. Hence, when comparing the numbers of DSWs in 1971–1992 with 1993–2004, *by year of approval*, it is preferable to allow some time lag after the later period to achieve a fair comparison. For example, eight of the drugs withdrawn in the US, and fourteen withdrawn in the UK, since the end of 1992 were approved in the

Table 1
Drug Safety Withdrawals 1993 to September 2008 (including re-instated drugs).

Year First Withdrawn patient exposure (M)[a]	Drugs generic (Trade Name) clinical target *other notes*	UK dates on market/ OTHER SCENARIOS	US dates on market/ OTHER SCENARIOS
1993 (0.01)	flosequinan (Manoplax) congestive heart failure	1992–1993	1992–1993
1993 (0.01)	nebacumab (Centoxin) sepsis	1991–1993	APPROVAL REFUSED
1993 (0.01)	Etretinate (Tegison-US) (Tigason-UK) psoriasis	1981–1993	1986–2002
1994 (0.01)	Remoxipride (Roxiam) schizophrenia/psychoses	1990–1994	NOT APPROVED (application withdrawn 1994)
1995 (0.001)	naftidrofuryl oxalate i.v. (Praxilene i.v) peripheral vascular disease *not NME*	1978–1995	NOT MARKETED
1995 (0.1)	Probucol (Lorelco – US) (Lurselle – UK) hypercholesterolaemia	1982–1997	1977–1995
1997 (0.1)	pemoline (Cylert–US) (Volital–UK) ADHD/hyperkinesias	*Pre-licencing*-1997	1975–2005
1997 (10.0)	Fenfluramine (Pondimin–US) (Ponderax–UK) obesity	*Pre-licencing*-1997	1973–1997
1997 (10.0)	Dexfenfluramine (Redux–US) (Adifax–UK) obesity *not NME*	1990–1997	1996–1997
1997 (1.0)	Troglitazone (Rezulin–US) (Romozin–UK) diabetes	1997–1997	1997–2000
1998 (1.0)	Terfenadine (Seldane) anti-histamine	1980– NOT WITHDRAWN	1985–1998
1998 (0.1)	Mibefradil (Posicor) hypertension/angina	1997–1998	1997–1998
1998 (0.01)	Bromfenac (Duract) acute pain	NOT MARKETED	1997–1998
1998 (0.01)	Tolcapone (Tasmar) Parkinson's *EU-reinstated*	1997–1998/ reinstated 2004- via EU-Centralised-Procedure (CP)	1998- NOT WITHDRAWN
1998 (0.01)	Sertindole (Serdolect) schizophrenia/psychoses *EU-reinstated*	1996–1998/ reinstated 2002- via CP	APPROVAL REFUSED
1999 (0.1)	Astemizole (Hismanal) anti-histamine	1983–1999	1988–1999
1999 (0.01)	Grepafloxacin (Raxar) pneumonia/bronchitis	1997–1999	1997–1999
1999 (0.1)	Trovafloxacin (Trovan) bacterial infection	1998–1999 via EU-CP	1998 - NOT WITHDRAWN
1999 (0.01)	rotavirus vaccine (Rotashield) rotavirus	1999–2000 via EU-CP	1998–1999
2000 (0.001)	Pumactant (ALEC) respiratory distress syndrome	1994–2000	NOT MARKETED

(*continued on next page*)

Table 1 (*continued*)

Year First Withdrawn patient exposure (M)[a]	Drugs generic (Trade Name) clinical target *other notes*	UK dates on market/ OTHER SCENARIOS	US dates on market/ OTHER SCENARIOS
2000 (1.0)	Cisapride (Propulsid–US) (Prepulsid–UK) gastro-oesophageal reflux	1988–2000	1993–2000
2000 (1.0)	alosetron (Lotronex) Irritable bowel syndrome *US-reinstated*	NOT APPROVED	2000–2000 reinstated 2002-
2001 (0.01)	Rapacuronium (Raplon) surgical muscle relaxation	NOT APPROVED	1999–2001
2001 (0.1)	Droperidol (Inapsine–US) (Droleptan–UK) anaesthesia/sedation	*Pre-licencing*-2001	1970- NOT WITHDRWN
2001 (0.001)	Levacetylmethadol (Orlaam) opiate addiction	1997–2001 via EU-CP	1993–2003
2001 (1.0)	Cerivastatin (Baycol–US) (Lipoba–UK) hypercholesterolaemia	1997–2001	1997–2001
2003 (0.1)	Nefazodone (Serzone–US) (Dutonin–UK) depression	1993–2003	1994- NOT WITHDRAWN
2004 (10.0)	Rofecoxib (Vioxx) arthritis	1999–2004	1999–2004
2005 (0.1)	co-proxamol (Darvocet) mild/moderate pain *not NME*	*Pre*-licensing-2005	1972- NOT WITHDRAWN.
2005 (0.01)	Natalizumab (Tysabri) multiple sclerosis/ Crohn's *US-reinstated*	2006- NOT WITHDRAWN via EU-CP	2004–2005/ reinstated 2006-
2005 (1.0)	Valdecoxib (Bextra) arthritis	2003–2005 via EU-CP	2001–2005
2005 (0.001)	hydromorphone hydrochloride-extended release (Palladone-SR) moderate/severe pain *not NME*	2003- NOT WITHDRAWN.	2004–2005
2005 (0.001)	Technetium (99m-Tc) fanolesomab (Neutrospec) appendicitis radiodiagnosis	NOT MARKETED	2004–2005
2007 (0.01)	Pergolide (Permax–US) (Celance–UK) Parkinson's	1990- NOT WITHDRAWN	1988–2007
2007 (0.01)	Tegaserod (Zelnorm) IBS/constipation	NOT APPROVED	2002–2007
2007 (0.01)	Aprotinin (Trasylol) surgical bleed suppressant	*Pre-licensing*-2007	1993–2007
2007 (0.01)	Lumiracoxib (Prexige) arthritis	2003–2007	NOT APPROVED
2008 (0.01)	Gatifloxacin (Tequin) bacterial infection	NOT MARKETED	1999–2008

[a] Estimated patient exposure in UK, US or both to decimal point in millions (e.g. 0.1 means 100,000s, 1.0 means millions).

Table 2
Absolute numbers of UK & US DSWs according to year of approval.

Period (years)	1971–1992 (22yrs)	1993–2004 (12 yrs)
US *absolute number (average per year)*	17 (0.8)	17 (1.4)
UK *absolute number (average per year)*	36 (1.6)	12 (1.0)

Table 3
Absolute numbers of UK & US DSWs according to year of withdrawal.

Period (years)	1971–1992 (22yrs)	1993–2004 (12 yrs)
US *absolute number (average per year)*	9 (0.4 per yr)	18 (1.5 per yr)
UK *absolute number (average per year)*	23 (1.0 per yr)	22 (1.8 per yr)

period 1971–1992, so in a quantitative comparison of DSWs by year of approval, those drugs would be counted in the earlier period, even though they are seen as withdrawals years later. Thus, our later comparison period, 1993–2004, allows a time lag to 2008 when counting DSWs by year of approval. For quantitative analyses by year of withdrawal, there is a straight comparison between the two periods 1971–1992 and 1993–2004.

Excluding re-instated drugs, Tables 2 and 3 show the absolute numbers of DSWs in the two countries in the two periods according to year of approval and withdrawal, respectively. These figures reiterate Abraham and Davis (2005) that from 1971 to 1992 the UK had over twice as many DSWs as the US, whether calculated by year of approval (UK/US ratio 36:17 = 2.1) or year of withdrawal (UK/US ratio 23:9 = 2.6). Regarding UK DSWs by year of approval from 1993 to 2004, Table 2 excludes five 'pre-licensing' drugs because they have no approval dates as such (so it could be that there were 17 UK DSWs from 1993 to 2004, rather than 12). Tables 2 and 3 show dramatic changes in the UK/US DSW ratio in 1993–2004 whether by year of approval (12:17 = 0.7 or 17:17 = 1.0 including all pre-licensors) or by year of withdrawal (22:18 = 1.2).

Evidently, there has been a change from twice as many DSWs in the UK as in the US during 1971–1992 to both countries having a similar number during 1993–2004. Tables 2 and 3 also demonstrate that most of this change results from many more DSWs in the US during 1993–2004 compared with 1971–1992. By year of approval US DSWs have almost doubled (1.4:0.8 = 1.75) and nearly quadrupled by year of withdrawal (1.5:0.4 = 3.75). By contrast, UK DSWs have increased much less (1.8:1.0 = 1.8 by year of withdrawal) or even fallen on one measure (1.0:1.6 = 0.6 by year of approval; 1.4:1.6 = 0.9, including pre-licensors).

2.2. Absolute numbers of DSWs and DSW rates

Some scholars and regulators contend that DSW *rate* (percentage of drugs withdrawn out of all those approved in any given period) is a better measure than absolute number of DSWs, thus implying that the public health problem of DSWs should only be weighed quantitatively relative to total numbers of drugs approved (Bakke et al., 1995; CDER, 2006; Jefferys et al., 1998; Tufts, 2005). However, a small number of DSWs, including drug disasters like Vioxx, could have more significant health implications than a large number of other drug approvals, especially if only a small proportion of such approvals are needed therapeutically (Angell, 2004; La Revue Prescrire, 2005). Relying solely on DSW rates, therefore, could underplay important problems in drug safety regulation.

In calculating them, scholars typically count only NMEs, so we *exclude* re-instated drugs and non-NMEs from our analyses of DSW rates (Table 1). Our temporal comparative analysis of DSW rates by year of approval for 1971-92 allows a four-year follow-up period to 1996, together with our estimate of the DSW rate for 1993–2004 allowing follow-up to 2008. By this method, DSW rates for 1971–1992 are 5.9%

(28/478) in the UK and 2.3% (10/439) in the US. We also estimate a US DSW rate of 3.9% (14/357) for 1993–2004. Hence, the US DSW rate increased from 2.3% to 3.9% - a growth factor of 1.7, almost exactly the growth factor of 1.75 we discovered when calculating the *absolute number* of US DSWs by year of approval. Evidently, whether one estimates DSWs by absolute numbers or NME rates, they have approximately doubled in the US in 1993–2004 compared with 1971–1992, so increases in US DSWs are not merely due to FDA approving more drugs.

We could not calculate the UK DSW rate for 1993–2004 because, shockingly, the MHRA was unable/unwilling to provide us with an accurate list of all NMEs. Nevertheless, from other sources, we estimate and compare the UK DSW rates for 1971-88 and 1989–1994 by year of approval, i.e. before and after MCA's industry fee expansion, acceleration of drug reviews and increased industry consultation. For this comparison, to be fair, we allow a fourteen-year follow up for the earlier period (1971–1988) because there are fourteen years to 2008 beyond the end of the later period (1989–94) during which drugs approved between 1989 and 1994 could be withdrawn. Using this method, the UK DSW rate for 1971-88 is 5.5% (20/364) and 4.3% (7/161) for 1989–94. Hence, the UK DSW rate by year of approval has decreased by a factor of 0.8 (4.3/5.5) in 1989–1994 compared with 1971–1988. This is similar to the 0.6 shrinkage factor in the *absolute number* of UK DSWs for 1993–2004 by year of approval. However, this must be weighed against the fact that the absolute number of UK DSWs *by year of withdrawal* has *grown* by a factor of 1.8. Overall, the precise quantitative extent of change in UK DSWs between 1971-1992 and 1993–2004 is equivocal but it is clear that it is relatively small compared with the unequivocal evidence of a marked increase in US DSWs in the later period by all measures.

Hence, the extent of DSWs in the two countries has, on both measures, *converged* considerably in 1993–2004 compared with 1971–1992. The convergence is due to the dramatic increase in US DSWs during the later period from a relatively low incidence in the earlier period, while the extent of UK DSWs in the later period has not changed much from its relatively high incidence in the earlier period. Taking six-year approval cohorts with fourteen years follow-up for UK approvals and four years follow-up for US approvals, Figs. 1 and 2 elaborate this convergence by showing that US DSW rates, by year of approval, are never as high as UK DSW rates, but after 1992 they rise sharply to 3.8% and by 2004 they are approaching UK rates (which are declining from 4.3%).

2.3. Beyond counting DSWs: divergent UK/US regulatory outcomes

We define a DSW divergent approval outcome as when a drug is approved and withdrawn in one country, but never approved or never marketed in the other country. A DSW divergent withdrawal outcome is

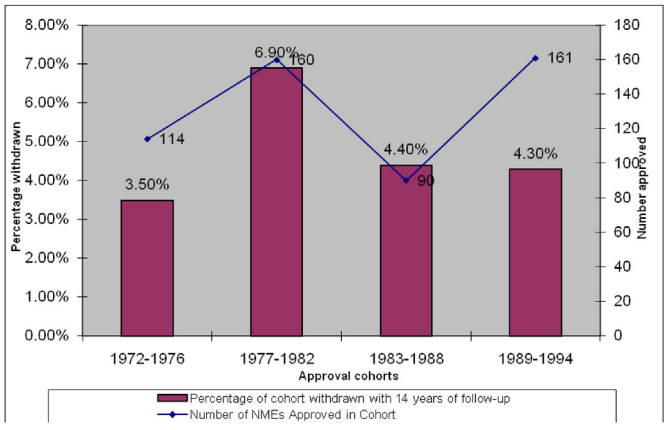

Fig. 1. UK trends in NME withdrawal rates allowing 14 years of follow-up for each approval cohort.

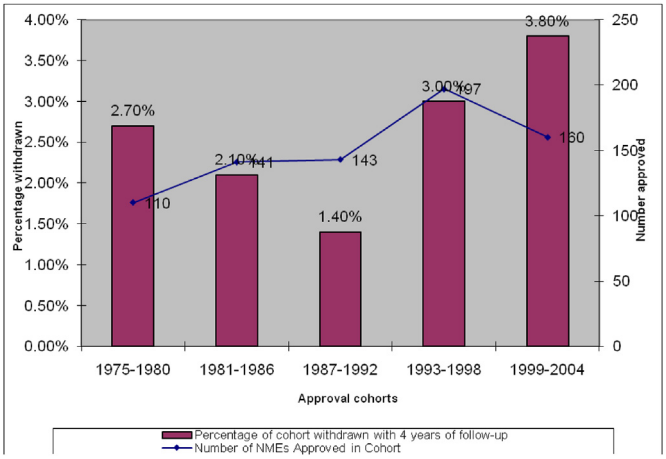

Fig. 2. US trends in NME withdrawal rates allowing 4 years of follow-up for each approval cohort.

when a drug is withdrawn in one country but either never withdrawn, or withdrawn more than one year later, in the other country. To further investigate the changing nature of drug safety regulation in both countries, we conducted a quantitative comparative analysis of divergent regulatory outcomes (approvals and withdrawals) in the period 1971–1992 with 1993–2004, allowing four-year follow-up to 2008 when analysing divergent approvals, *according to year of divergent approval outcome*.

For 1971–1992, we calculated 21 divergent regulatory outcomes (divergent approvals and withdrawals) pertaining to a total of 27 DSWs. Excluding re-instated drugs, from 1993 to 2004, there were 17 divergent regulatory outcomes relating to 26 DSWs. Figs. 3 and 4 show a breakdown of the different types of divergent regulatory outcomes for the two periods. Divergent approval/marketing outcomes in the US (i.e.

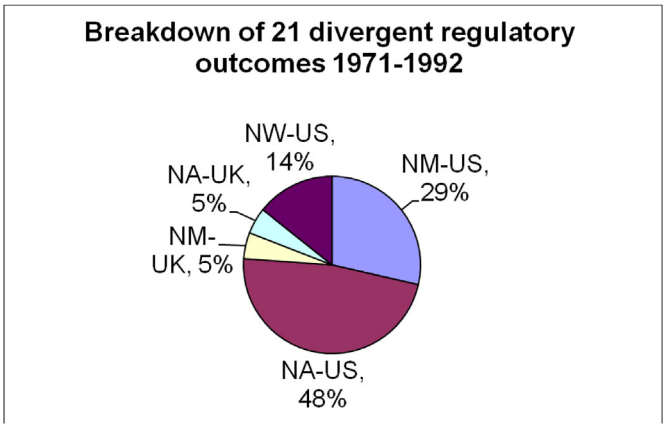

Fig. 3. Divergent regulatory outcomes 1971–1992. **NM-US – Not Marketed in US:** Approved and later withdrawn in UK but never marketed in US. Unknown whether approval sought in US. **NA-US – Not Approved in US:** Approved and later withdrawn in UK. Approval sought in US but drug never marketed there. **NM-UK – Not Marketed in UK:** Approved and later withdrawn in US but never marketed in UK. Unknown whether approval sought in UK. **NA-UK – Not Approved in UK:** Approved and later withdrawn in US. Approval sought in UK directly (or via EU regulatory procedure) but drug never marketed there. **NW-US – Not Withdrawn in US:** Safety withdrawal in UK but left on US market (or discontinued in US by manufacturer, but *not* for safety reasons). **DW-US – Delayed Withdrawal in US:** At least a year's delay between withdrawal in UK and subsequent withdrawal in US. **NW-UK – Not Withdrawn in UK:** Safety withdrawal in US but still marketed in UK (or discontinued in UK by manufacturer, but not for safety reasons). **DW-UK –Delayed Withdrawal in UK:** At least a year's delay between withdrawal in US and subsequent withdrawal in UK.

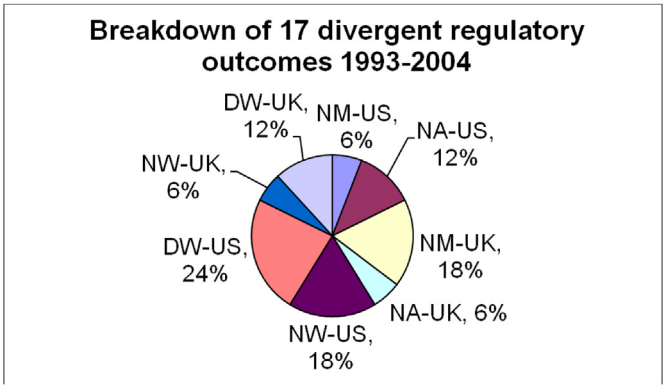

Fig. 4. Divergent regulatory outcomes 1993–2004. **NM-US – Not Marketed in US:** Approved and later withdrawn in UK but never marketed in US. Unknown whether approval sought in US. **NA-US – Not Approved in US:** Approved and later withdrawn in UK. Approval sought in US but drug never marketed there. **NM-UK – Not Marketed in UK:** Approved and later withdrawn in US but never marketed in UK. Unknown whether approval sought in UK. **NA-UK – Not Approved in UK:** Approved and later withdrawn in US. Approval sought in UK directly (or via EU regulatory procedure) but drug never marketed there. **NW-US – Not Withdrawn in US:** Safety withdrawal in UK but left on US market (or discontinued in US by manufacturer, but *not* for safety reasons). **DW-US – Delayed Withdrawal in US:** At least a year's delay between withdrawal in UK and subsequent withdrawal in US. **NW-UK – Not Withdrawn in UK:** Safety withdrawal in US but still marketed in UK (or discontinued in UK by manufacturer, but not for safety reasons). **DW-UK –Delayed Withdrawal in UK:** At least a year's delay between withdrawal in US and subsequent withdrawal in UK.

drugs not approved/marketed in the US, but approved and withdrawn in UK) account for 77% of all divergent regulatory outcomes in 1971–92, but only 18% in 1993–2004. Regarding divergent approval/marketing outcomes in the UK (i.e. drugs not approved/marketed in the UK, but approved and withdrawn in the US), they accounted for just 10% of all divergent regulatory outcomes in 1971–92, but grew to 24% in 1993–2004.

Divergent *withdrawal* decisions in the US (i.e. drugs withdrawn for safety reasons in the UK but left on the US market), accounted for just 14% of all divergent regulatory outcomes in 1971–1992, but climbed to 42% in 1993–2004. Divergent withdrawal decisions in the UK (drugs withdrawn for safety reasons in the US but left on the UK market) did not exist (0%) in 1971–1992, but accounted for 18% of all divergent regulatory outcomes in 1993–2004.

These findings demonstrate that in 1971–1992 the DSW picture was dominated by drugs being approved/marketed by UK regulators and then having to be withdrawn in the UK, but never approved/marketed in the US. From 1993 to 2004 that dominant picture no longer obtained. The picture changed to be most strongly characterised by drugs being withdrawn from the UK market for safety reasons, but those same drugs being left on the US market. That scenario occurred three times more often during 1993–2004 than in 1971–1992.

Moreover, during 1993–2004, drugs were more often approved/marketed and then withdrawn in the US, but never approved/marketed in the UK (24%), than they were approved/marketed and then withdrawn in the UK, but never approved/marketed in the US (18%). Indeed, in 1993–2004, drugs were more than twice as likely to be left on the US market after having been withdrawn in the UK (42%) than they were to be left on the UK market after having been withdrawn in the US (18%), and they were three times as likely to be left on the US market after having been withdrawn in the UK (42%) compared with 1971–92 (14%).

Assuming that non-approval of a drug in one country which is later withdrawn in another country implies *greater* patient protection in the former country, and failure by the latter country to withdraw a drug that has been withdrawn for safety reasons in the former country implies *less* patient protection, then our analysis of divergent regulatory outcomes strongly suggests that FDA performance in protecting US citizens from unsafe drugs deteriorated in 1993–2004 relative to its performance during 1971–92, *and* relative to the performance of the UK regulatory authorities. By contrast, the patient-protective performance of the UK regulatory authorities improved relative to FDA, and to pre-1993 UK performance in keeping unsafe drugs off the market, but deteriorated relative to UK pre-1993 performance in terms of its decisions on whether or not to withdraw drugs.

Yet, such assumptions may not necessarily be justified because non-approval may not necessarily result from a regulatory agency spotting safety signals missed by another regulatory authority or from having higher approval standards. Other factors, such as post-marketing safety information from other countries, while deciding about approval could be involved. Such complex matters can only be settled by examining the regulatory case-histories of the individual drugs, to which we now turn.

2.4. Beyond quantitative associations: explaining the changes in UK/US DSW trends

Drawing on our qualitative analysis of the regulatory case-histories of each drug, we explain the above trends by systematically examining six hypotheses (H1–H6). Most attention is on the US because it is dramatic changes in US DSWs that mostly account for changes in the UK/US comparative trends.

H1: The larger number of US DSWs during 1993–2004 is explained by FDA becoming less tolerant of post-market drug risks than it was in 1971–92, and than the UK was in 1993–2004.

Our research does not support this hypothesis (advanced publicly by some FDA managers) because FDA permitted marketing of troglitazone, tolcapone, trovafloxacin and levacertylmethadol for several years in the US after they had been withdrawn in the UK by UK/EU regulatory authorities. In fact, we found that FDA was *more* tolerant of post-market drug risks in 1993–2004 than it was during 1971–1992, and than EMA was during 1993–2004. This is probably because under PDUFA from 1993 to 2004, FDA was not permitted to spend PDUFA funding on post-marketing safety regulation (GAO, 2002:7) It is less clear whether MCA *consistently* adopted a more precautionary approach to post-market safety problems than FDA during 1993–2004. MCA did so in the cases of pemoline, troglitazone and droperidol, but permitted marketing of terfenadine and probucol after their US withdrawal.

H2: There has been an increase in US DSWs from 1993 to 2004 because most serious drug toxicity leading to withdrawal can only be discovered post-marketing and during 1971–1992 drugs were typically marketed first in UK/Europe so that FDA had the benefit of post-marketing safety information from UK/Europe in that period, but in 1993–2004 the US was usually the market of first launch so FDA was deprived of such post-marketing safety information.

This hypothesis was also put forward by some FDA managers. UK and US regulators routinely informed each other about DSW decisions and shared post-marketing safety data that informed decisions, but frequently still made different decisions (Abraham and Sheppard, 1999). However, Abraham and Davis (2005) demonstrated that for 40% (10/25) of all DSWs in the UK or US from 1971 to 1992, there was a signal of the safety problems that ultimately led to drug withdrawal contained in the *pre-market* data submitted for approval. Our analysis of regulatory approval case histories of drugs withdrawn in 1993–2004 shows that signals of toxicity were present in data submitted before approval for *most* of those products. Table 4 shows that, for the twenty drugs that were withdrawn in the UK or US from 1993 to 2004 and approved in the UK or US after 1988, pre-approval data submitted to the regulators contained signals of the safety problems that ultimately led to drug withdrawal in fifteen of those cases (75%). The figure is 71% (12/17) if the three re-instated drugs (alosetron, tolcapone and sertindole) are excluded. Evidently, such pre-market signals were

Table 4
Presence, detection and approval of safety problems leading to withdrawal of drugs approved 1989–2004.

Drug	Reason for withdrawal	PPMT	DMPT (by)	FDAA&M	UKA&M
remoxipride	aplastic anaemia	no	no	no	yes
nebacumab	excess mortality	yes	yes(FDA) unknown(CHMP)	no	yes
pumactant	excess mortality	no	no	no	yes
sertindole	long-QT-arrythmia/torsades de-pointes	yes	yes(FDA) unknown(MCA)	no	yes
flosequinan	excess mortality	yes	yes(FDA) unknown(MCA)	yes	yes
cisapride	long-QT/torsades	possibly	possibly(FDA) no(MCA)	yes	yes
levacetylmethadol	long-QT/torsades	yes	yes(FDA) yes(CHMP)	yes	yes
nefazodone	liver toxicity	no	no	yes	yes
dexfenfluramine	primary-pulmonry hypertension (PPH) & cardiac valvulopathy	yes(PPH) possibly (valvulopathy)	PPH yes(FDA) valvulopathy no(FDA & MCA)	yes	yes
cerivastatin	rhabdomyolysis	yes(0.4 & 0.8 mg)	yes(FDA) possibly(MCA)	yes	yes
mibefradil	long-QT/drug interaction (DI)	yes	QT yes(FDA) DI yes(MCA)	yes	yes
grepafloxacin	long-QT/torsades	yes	yes(FDA) unknown(MCA)	yes	yes
troglitazone	liver toxicity	yes	yes(FDA) unknown(MCA)	yes	yes
tolcapone	liver toxicity	yes	yes(FDA) yes(CHMP)	yes	yes
trovafloxacin	liver toxicity	yes	yes(FDA) yes(CHMP)	yes	yes
rotavirus vaccine	intussusception	yes	yes(FDA) yes(CHMP)	yes	yes
rofecoxib	myocardial infarction/stroke	probably not	no(FDA) no(MCA)	yes	yes
bromfenac	liver toxicity	yes	yes(FDA) unknown(MCA)	no	yes
rapacuronium	bronchospasm	yes	yes(FDA) unknown(EU)	no	yes
alosetron	ischaemic colitis	yes	yes(FDA) possibly(CHMP)	no	yes

PPMT: reason for DSW present in pre-market testing data submitted.
DMPT: reason for DSW detected by regulatory agency in pre-market testing submitted before approval/marketing in that country.
FDAA&M: FDA-approved and marketed in US.
UKA&M: Approved on to UK market by British/EU regulatory systems.

present for *an even higher proportion* of DSWs in 1993–2004 than in 1971–1992. Furthermore, Table 4 shows that, *in all fifteen of those cases,* FDA detected those safety signals in its pre-approval assessment, but nonetheless approved ten of them (67%) on to the US market. Mostly, these were *strong* signals of safety problems recognised by regulators with minimal doubt that the toxicities were drug-related. By contrast, in 1971–1992, FDA approved only 25% (2/8) drugs when it had detected in pre-market assessment the safety problem that ultimately led to withdrawal (Abraham and Davis, 2005). We found that FDA approved more unsafe drugs in 1993–2004 than in 1971–1992 not principally because the safety problems could not be detected, but rather because of a more permissive risk-benefit interpretation placed upon them by the regulatory agency upon detection. Thus, H2 must be rejected.

H3: Since the early 1990s, FDA has become more willing to approve less safe drugs or leave such drugs on the market, rather than withdraw them, because patient pressure for access to new drugs has grown in the US and is more powerful than in the UK/EU.

Along with some arguments by Carpenter (2004, 2010) and Daemmrich (2004), several senior FDA officials have suggested that AIDS activists' criticisms of the agency in the late 1980s/early 1990s for not approving AIDS drugs fast enough shifted FDA's orientation away from its earlier, more risk-averse 'paternalistic' approach to drug regulation (disease-politics theory). However, this does not explain why FDA extended its less risk-averse permissive regulatory approach during 1993–2004 to *all* new drugs, the majority of which according to FDA's own evaluations, offered little or no therapeutic advance (Davis and Abraham, 2013). Based on our analyses of internal regulatory documents, including public expert advisory committee meetings, we found that patient pressure influenced FDA's post-marketing safety regulation of the IBS drug, alosetron, but had little significance in the cases of tolcapone, trovafloxacin and levacetylmethadol, which were either not withdrawn or had a delayed withdrawal in the US (Woodcock, 2002). Although patient pressure was less significant in the UK, evident from its absence from decision-making in our case-history analyses, we found scant evidence to support H3.

H4: During 1993–2004, UK/EU regulators' reluctance to non-approve or withdraw unsafe drugs has grown slower than at FDA because post-market risk management was more difficult and less used in the EU due to Member State differences in the organisation/delivery of healthcare.

EMA and FDA sometimes require manufacturers to conduct specific studies in order to inform regulatory management of post-market drug risks. We found no evidence to support conjecture H4 (put forward by some UK and EU regulators). In the most relevant cases of tolcapone, trovafloxacin and levacetylmethadol, it was the risk management *tools* (e.g. liver function and ECG monitoring), accepted by FDA, which were judged to be inadequate by the EMA-CHMP because the latter insisted that the manufacturers should provide clinical evidence that those drugs benefited a sub-group of patients intolerant/unresponsive to alternative therapies. These were not cases of international differences in regulatory-management capability, but rather cases where EMA-CHMP imposed higher evidential standards than FDA to support manufacturers' risk management plans (e.g. EMA [1999]).

H5: FDA and UK regulators approved and withdrew more unsafe drugs during 1993–2004 than in 1971–1992 because of faster drug review times post-PDUFA in the US and after MCA's policy of

shortening review times in the UK.

The Institute of Medicine (2006) argues that, under PDUFA, FDA scientists have less time to review new drug applications, so are more likely to miss signals of safety problems. We found some cases (troglitazone and rapacuronium) where PDUFA deadlines caused FDA to rush approval leading to problematic regulatory evaluations, but H5 does not fit most of our cohort. As explained, strong safety signals *were detected* by FDA reviewers *before approval* of many DSWs, so the main explanation was not that safety signals were missed. Moreover, review times for many US DSWs were longer than average FDA review times for all drugs approved in the same year: nefazodone (40 months, year-average 23 months); dexfenfluramine (35 months, year-average 18 months); bromfenac (30 months, year-average 15 months); tolcapone (20 months, year-average 13 months). Hence, H5 makes only a minor contribution to explaining our trends.

Regarding the UK, in some cases (e.g. troglitazone), over-reliance on industry summaries of data led MCA to accept company interpretations of safety/efficacy data challenged by FDA. Yet, we found no compelling evidence that post-1988 MCA cuts to review times led to overall increases in UK DSWs, though during 1993–2004, UK regulatory authorities were more likely than in 1971–1992 to leave less-safe drugs on the UK market after withdrawal in the US. That permissive tendency might have suppressed observable increases in UK DSWs.

H6: During 1993–2004, FDA became more willing than in 1971–1992 to approve less-safe drugs on to the market and/or leave such drugs on the market, rather than withdraw them, because of a change in its political and institutional culture.

This is the best explanation for the dramatic change in US DSW regulatory outcomes and has been raised by many FDA scientists. Such change was multi-faceted, not confined solely to reduced review times or industry fees *per se*. Industry fees to fund FDA drug review markedly increased the extent to which the agency regarded industry, rather than the American public, as its 'client'. FDA internal documents suggest that the primary focus of the agency became meeting PDUFA deadlines to *approve* drugs (Federal Register, 2000). Crucially, this shift in institutional culture led to more permissive safety and risk-benefit assessments by regulators.

We found FDA regulators were withdrawn from drug reviews and their recommendations for non-approval were over-ruled (as occurred with troglitazone and bromfenac). Some FDA scientists have suggested in public testimony that recommendations to approve drugs were not questioned, whereas recommendations to non-approve were always interrogated and reviewers critical of industry submissions were unlikely to be promoted because FDA managers during 1993–2004 increasingly prioritised getting drugs on the market (Institute of Medicine, 2006).

That FDA reviewers felt increasingly pressured by agency management to approve drugs during 1993–2004 is supported by three surveys. One in 1998 to 172 medical reviewing officers, of whom 53 responded, found that 64% (34/53) believed that pressure on them to approve new drugs was 'somewhat greater' or 'much greater' compared with before 1995. Nineteen (36%) identified 27 drug approvals they had reviewed during the past three years that they thought should not have been approved, while only five (9%) identified 6 drugs they thought should have been approved in those three years, but were not. The survey recorded 32 occasions of medical officers being asked to withhold criticism of a drug so as not to jeopardise its approval (Public Citizen, 1998). A second by FDA itself in 2001 reported that over one-third of FDA-CDER staff felt that non-approvals were stigmatised in FDA, while a third survey by US Department of Human and Health Services (DHHS) Office of the Inspector General in 2002 found that 72 of 401 (18%) FDA scientists were pressured to recommend approval of drugs 'despite reservations about safety/efficacy/quality' (DHHS, 2003).

H6 is also favoured because it can account for the fact that, despite safety signals often detected by FDA scientists in 1993–2004, the drugs were nevertheless approved on to the US market, and that this happened *more* than it did during 1971–1992. Furthermore, change in FDA's regulatory culture, including introduction of programmes to risk manage drugs on the market instead of withdrawing them, explains our finding that FDA delayed withdrawal of unsafe drugs from the market much more during 1993–2004 than 1971–1992 (FDA, 1999).

Yet H6 says nothing about why political/institutional changes to the UK regulatory authorities (increased industry-fee dependence, reduced review times, and expanded responsiveness to industry) did not generate similar transformations in UK DSW outcomes during 1993–2004 to those seen in the US. One explanation is that, before 1989, the British regulatory authorities were already half-funded by industry fees, had some of the fastest review times in the Western world, and already saw their role as being very industry-responsive (Abraham, 1995:66-77). Consequently, unlike the US, the post-1988 changes at MCA did not amount to correspondingly dramatic shifts in political and institutional culture. Additionally, insofar as the Executive arm of the British Government set priorities for UK drug safety regulation, they have not changed dramatically between 1976 and 2004 (House of Commons Health Committee, 2005). Indeed, during 1993–2004, the UK regulatory agency moderated its high level of industry-responsiveness by introducing constraints on industry conflicts of interests of its expert advisors. Thus, the bureaucratic, financial, legislative, and political/ideological changes that explain the dramatically altered US DSW outcomes post-1992 are either absent or much less marked in the UK from 1993 to 2004.

A second explanation is the establishment of EMA in 1995 after which many new drugs entered the UK market via centralised EU regulatory decision-making. EMA applied more stringent safety regulation than FDA in several cases (e.g. levacetylmethadol, tolcapone, and trovafloxacin) in 1993–2004. The relatively permissive UK regulatory approach during 1971–1992 was, therefore, partly attenuated after 1995 by EMA-CHMP, which partly offset internal organisational tendencies towards greater industry responsiveness at MCA from 1989.

3. Conclusion and policy implications

1993–2004 saw a *quantitative* change from the UK having twice as many DSWs as the US during 1971–1992 to both countries having a similar number, though the UK continues to have slightly more DSWs in the later period on most measures (partly explained by FDA leaving more unsafe drugs on the market). This convergence is almost entirely due to the dramatic increase in US DSWs in the later period, while UK DSWs have remained relatively stable at their comparatively high 1971–1992 levels. The *nature* of the DSW regulatory landscape also changed from one in 1971–1992 dominated by unsafe drugs being approved/marketed in the UK and then having to be withdrawn in the UK (but never approved/marketed in the US) to a situation in 1993–2004 strongly characterised by unsafe drugs being withdrawn from the UK market and those same drugs being left on the US market. Furthermore, FDA approved more unsafe drugs in 1993–2004 than 1971–1992 not principally because the safety problems could not be detected pre-approval, but rather because of the more permissive risk-benefit interpretations adopted by the agency upon pre-approval detection. To a first approximation, the convergence of the two regulatory systems for drug safety in 1993–2004 may be characterised as FDA becoming much more like the UK regulatory system (of 1971–92 and 1993–2004) than the FDA of 1971–92.

Assuming the fundamental purpose of drug safety regulation is protection of patients from unsafe drugs then FDA performance considerably worsened during 1993–2004 compared with 1971–1992, while there was much less erosion (from a relatively low base) in such UK regulatory performance. The altered political and institutional culture at FDA during 1993–2004 is the best explanation for the agency's worsening performance. This explanation cannot be reduced solely to shortened drug review times or industry fees *per se*.

Rather, it must be seen in the transformational context of the post-

PDUFA regulatory culture in which FDA funding (via industry fees) became dependent on industry-Congress-defined performance goals to *approve* drugs faster and view industry as a partner/client in facilitating the availability and *maintenance* of drugs on the market as opposed to a more adversarial/critical stance towards manufacturers' claims about the safety (and efficacy) of their products. This then led to an increased tendency, relative to 1971–1992, to adopt more permissive and less precautionary interpretations of the substantive risk-benefit judgements about individual drugs – overplaying benefits and rationalising how risks could be managed on the market within *both* pre-market assessment and post-market safety evaluation. British drug regulatory culture, by contrast, exhibited a picture of much more continuity between the two periods.

Our discovery that both regulatory agencies' performance deteriorated by leaving unsafe drugs on the market more during 1993–2004 than in 1971–1992 raises the spectre that had there not been this more permissive post-market regulatory stance in the later period, there might well have been more DSWs in both countries during 1993–2004. In short, our quantitative analysis of DSWs probably understates the deterioration of pre-market drug safety regulation in the later period. Our conclusion that US drug safety regulation declined in the later period is supported by Olson (2008, 2013), who demonstrated very significant increases in the number of serious and fatal adverse drug reactions (per drug) reported by US healthcare professionals during 1990–2004.

Evidently, FDA performed significantly better in drug safety regulation during 1971–1992 than during 1993–2004 and better than the UK in either 1971–1992 or 1993–2004. The policy implication is that, as a first step to improve drug safety regulation, the UK and US governments should both re-orientate their regulatory cultures to be more compatible with the FDA model of 1971–1992 (not that that model was flawless).

The main limitation of this study is that regulatory case-history data were much less extensive in the UK (due to state secrecy) than in the US, making our judgements about UK regulators' pre-approval knowledge more difficult (see Table 4). A second limitation in relation to overall drug regulatory policy is the safety focus. Overall drug regulation in the interests of public health must also weigh the safety deficit of 1993–2004 in both countries (relative to FDA in 1971–1992) against possible benefits of faster approval of new drugs during 1993–2004. However, research on pharmaceutical innovations (NMEs) shows that the number of NMEs offering significant therapeutic advance approved by FDA between 1993 and 2004, *actually declined*, and that only about 10% of NMEs marketed in the US or Europe represented therapeutic advance (Angell, 2004; Abraham and Davis, 2007; Davis and Abraham, 2013; Light and Lexchin, 2012; Van Luijn et al., 2010:445). Hence, deterioration in safety regulation was not compensated for by faster access to more therapeutically important innovations. Rather, deteriorating safety regulation went hand in hand with expedited approvals that did not drive a growth in therapeutically valuable innovations available to patients. Given this and based on our empirical findings, one can confidently reject neo-liberal and disease-politics theories as inadequate accounts of regulatory change between these two periods, but our findings are consistent with corporate bias and capture theories.

Following the major drug safety disaster of Vioxx in 2004, Governments implemented drug safety reforms, but focused solely on post-marketing. The 2007 US Food and Drug Amendments Act asserted FDA powers to compel post-market safety studies and label changes. FDA was empowered to use PDUFA funds for post-marketing safety surveillance, such as Sentinel systems through which the agency contracts such surveillance to university-based researchers with access to large-scale healthcare databases in order to detect safety signals. However, our findings imply that both UK and US regulatory agencies are on a trajectory of increasingly leaving drugs on the market even after detection of safety problems, and in the US increasingly permitting drug approval despite major safety signals being evident in pre-market regulatory assessment. FDA's reluctance to withdraw products from the market, and instead issue safety warnings to limit product use to specific patient sub-populations has continued beyond 2004 (Moore et al., 2012). Furthermore, accelerated pathways to drug approval based on less safety data has continued beyond 2004 unabated and would seem to undermine detection/investigation of safety signals, while using 'patient demand' (disease-politics theory) as an unwarranted ideological legitimation for such policies (Davis and Abraham, 2013). The post-Vioxx reforms, which merit separate research, do not seem to address these problems. Rather, what is required is a re-shaping of regulatory culture into a less permissive approach to prescription drug safety (and benefit) assessments via composite political changes in Executive mission, legislative oversight, and public accountability that prioritise drug safety over responsiveness to industry interests and approval deadlines. Yet, in both countries, much of the regulatory cultures of 1993–2004 remain and are likely to converge further due to alignment of their safety data requirements and regulatory standards under the International Conference on Harmonisation since 2013 (Wiktorowisz et al., 2018). Consequently, regulation protecting citizens from unsafe drugs may continue to be sub-optimal.

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CRediT authorship contribution statement

John Abraham: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Writing - original draft, Writing - review & editing. **Courtney Davis:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Writing - original draft, Writing - review & editing.

Declaration of competing interest

None.

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